Russell

CALIFORNIA INSTITUTE OF TECHNOLOGY
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Dr.Joshua Lederberg,
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Dear Josh,

Thanks ever so much for your recent interesting letter, which finally caught up with me here at Cal Tech. More than one geneticist is responding to the call of the West, but in my case it is a temporary response, as I'm spending a year's Sabbatical with a Guggenheim fellowship to write a monograph on present status and potentialities of mammalian physiological genetics-- so far I'm still catching up on writing the papers that should have been out before I left, but pretty soon I hope to really dig in.

The department which is developing at Stanfprd sounds really something! I greatly admire Cliff Grobstein, and it sounds to me as if the combination of interests and intelligences which you'll have will be splendid. I find it a bit hard to state exactly what geneticists would at present be most interested in exploring deeply the "genetics of somatic cells". Coming in to your set-up, I would think such a person would be better to come equipped with some experience in and knowledge of mammalian material, which, as you said at Madison last spring, is the material of choice for such studies. (Conversion can be in either direction, to or from other parts of mammalian genetics; in your case, you have so much to offer in thinking about large populations of cells parallel to microbial populations, the new man would be more useful adding practical knowledge of the kinds of variable characters available in experimental mammals, and something of physiology, for example). A man who probably would not be interested, since he has just shifted into a job he thoroughly enjoys at Wistar, and has a wife in U.of Penn.Med.School, is Willys K. Silvers, with whom I have published, who got his Ph.D. with Sewall Wright, and was with Herman Chase on a postdoctoral, and then with me at Jackson Lab until this Wistar possibility came up. A man who might very well be interested is Sam L. Scheinberg, originally from the stamping-ground you are leaving(Ph.D. with Irwin). He is recommended by Ray Owen, who knew him at Oak Ridge last year. After some preliminary skirmishing, involving asking for too ambitious equipment, etc., to study genetics of somatic cells in bone-marrow implants, he eventually worked at Oak Ridge with Kim Atwood, and, according to Ray, really clicked beautifully there, so that if he had not made other commitments Oak Ridge would have been delighted to have had him carry on Kim's projects when he left. Obviously you can find out more about this man-- his name, by the way, is Sam L. Scheinberg-- by contacting either Ray or Kim Atwood. He is now located temporarily at the Agriculture Research Service, USDA, Animal Husbandry Division, Beltsville, Md., and is probably going into chicken blood groups.

Russell T.

Another man who might very well fit into your program is Jack Stimpfling, another recent Ph.D. of Irwin's, who is at present starting the second year of a postdoctoral fellowship with George Snell at the Jackson Lab. He is a very fine young immunogeneticist, and is also much interested in all

aspects of physiological genetics. He has an excellent organized mind, and I've found him very interesting to discuss with. One thing he would love to do is seek for evidences of genetic change in mammalian somatic cells, though I think he had in mind more changes analagous to transduction. We used to argue extensively as to how you would go about distinguishing different types of genetic change in somatic cells, and what test systems could be evolved for finding the aberrant cells, and, finally, what role they could possibly play in either development or evolution. (I'm the sceptic, not he!) He has already had considerable experience with histocompatability and with tissue and tumor transplantation, which would be very valuable in your proposed area of investigation.

Beyond these suggestions, my next idea would be to consult Herman Chase, if you have not already done so. His boys have a good grasp ofphysiological genetics. One recent product who has an excellent reputation, though I personally do not know him, is Lou Pierro, whose work has been largely with physiological genetics of pigmentation. As you continue in your search for a colleague trained in experimental mammalian genetics, you'll probably become aware, as us "oldsters" in the field already are, of the numerical deficit of new men in this field. The trouble, sir, lies with you guys who offer material where results come so fast and with such large numbers!

I'm not just being protective in not suggesting my closest present collaboratc in this type of work(at Jackson Laboratory, I mean). Seldon Bernstein is an excellent investigator, and marvelous for me to work with, but his basic interests are physiological, in homeostatic mechanisms, etc., rather than in genetic changes among the populations of cells.

Now about mutation and segregation in hematopoietic tissues: although Law, of course, has excellent evidence of selection in transplanted leukemias of both resistant and dependent mutant lines of cells(to a particular chemotherapeutic agent, of course), the situation is not that clear in W-series mutants. You pointed out two possibilities: WW to Ww mutation. About that, the survivors whose RBC, etc., we have studied are still WW, judging by size and numbers of their erythrocytes: I'm now quoting part of my Montreal squib, which is not published, really, of course, but the abstract is on pg.244, Vol.II, Proc. Xth Int.Genet.Congress-- Russell, Bernstein and Smith, Permanent Implantation and Continuing Function of Normal Blood-forming Tissue in Genetically Anemic Hosts. In comparing the blood-picture of 4 surviving(spont.) WW individuals from the WC inbred strain with that of 4 WWs which lived after receiving an implant of ww embryo hematopoietic cells, I had the following chart:

Untreated spont.survivors, WW-WC (13/132 live 40+ days)				Implanted WW-WC (2/6 surv.)				Implanted WW-WB (2/6 surv.)		
age	no.	RBC/mm^3 x 10^{-6}	MCV	age	no.	RBC/mm^3	MCV	age	no.	RBC/mm^3	MCV
0-1d.	26	1.68	107						1a	4.83	62
					1a	9.77	40	45	1b1	1.78	41
60d.	4	3.98	72	45d.	1	8.41	46	75	1b1	0.69	42
120d.	3	4.79	70	105d.	1a	11.99	36	105	1a	10.06	40
240d.	2	3.67	86	210d.	1a	9.44	42	210	1a	8.24	38
								310	1a	7.40	45

Thus although the implanted surviving WW anemics quickly attained the erythrocyte picture of normals(ww) the survivors(at least all those tested)

of the spontaneous type still are extremely anemic and macrocytic, thus there blood picture definitely suggests continued functioning of WW cells. This is all there is so far. There is, however, lots of evidence, that ww hematopoietic cells, if present, will swamp the blood picture, since they form blood so much faster than WW or WW^V cells. This is to me a fascinating story, and I plan to get deeper into it. As for a question you put about WW^V mutating to W^VW^V, it is possible, but I have no way of testing for it.

Still another question you asked: combinations with small numbers of ww cells. Isotopic tagging is all I have been able to think of yet, and I hope some day to try this, probably using Fe^{59}, which I have used in studying embryonic blood-formation already, so know I can mark embryo liver cells. Histocompatibility labels offer a lot of problems, since so far we have not been able to make any homologous implants, nor are we proficient enough to get the numbers that would be necessary for the kind of an experiment you outlined(getting a few $H_2^aH_2^a$ cells from $H_2^aH_2^b$ donor into $WW\text{-}H_2^aH_2^a$ host). Besides, if it's a WW host, it's probably a baby, and you'd be more apt to be dealing with an induced tolerance-- see what I mean about it's being a good idea to get a guy familiar with mammalian quirks?

One final question of yours(you're very good at this, you know): how about repeated chimeric contamination? The results of implantation without radiation, in which ww cells completely dominate the blood picture, as in the chart, suggest that this as well as mutation could be the explanation if the blood picture of survivors approaches that of normals, but the fact remains that the few spontaneous survivors we have tested don't have a ww blood picture.

A completely different subject for the ending: One of my activities supported by the Guggenheim fellowship is visiting medical genetics departments, especially since man is a mammal, and some of the nicest physiological work is being done in studies of human metabolic errors. I have forgotten whether or not you saw my application for this, but a place I asked to visit was the Medical Genetics Dept.of the U.of Wisconsin, and I rather thought I might do this on my way back east next summer. Of course, I have meanwhile gotten some idea of what's up there, and have enjoyed very much becoming familiar with the work of Newton Morton, but I feel another visit would be more suitably to the place where you will be located. When do you expect to set yourself up at Stanford? Would it be possible for me to visit your department any time while I'm here on the west coast? I very much hope this will be a possibility.

By the way, Newton Morton's a very smart guy. You ought to try to latch on to him. I suppose you'd have to have IBM equipment enough to fill 20 buildings, but I really think he knows what to do with it!

With this letter I'm enclosing the only really published article on implantation of blood-forming tissue from ww into radiated WW^V. The material in the Genet.Cong.abstract is at present being turned into 3 articles which I'll try to get to you once I've gotten them written and published!

Hope you find just the experimental geneticist you want,

Sincerely,

Tibby Russell